REMARKS

Claims 53-67 and 70-72 presently are pending and under consideration. The outstanding rejections are addressed in the order in which they appear in the Office action.

Rejections Under 35 U.S.C. § 112, 2nd Paragraph

According to pages 2 and 4 of the outstanding Office action, claims 53-67 and 70-72 presently stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as his invention. The Office action states "instant claim 53 discloses no sufficient explanation or definition of the alleged value 'Dv'." The Applicant respectfully traverses this rejection.

The terms "Dv10" and "Dv50" in claim 53 are art-recognized parameters used to characterize liquid spray plumes. Indeed, the Ward-Smith publication, which is currently being relied upon by the Examiner, refers to Dv10 and Dv50 as a way to characterize liquid spray plumes. See page 3 of Ward-Smith in Nasal Spray Testing, Pharmaceutical Technology Europe (2002). In accordance with the art-recognized meaning of Dv10, the term Dv10 refers to the diameter of a spray droplet at which 10 percent of the spray volume is in drops smaller than this diameter, and 90 percent of the spray volume is in drops larger than this diameter. The term Dv50 refers to the diameter of a spray droplet at which 50 percent of the spray volume is in drops smaller than this diameter, and 50 percent of the spray volume is in drops larger than this diameter. In summary, Applicant submits that Dv10 and Dv50 are standard terms that were known and used by those skilled in the art at the time the invention was made and, as a result, do not need to be defined in the specification.

Accordingly, Applicant respectfully requests that the rejection of claims 53-67 and 70-72 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

Rejection of Claims 53-59, 62-67, 70, and 71 Under 35 U.S.C. § 103(a)

According to pages 2, 3, and 5-8 of the outstanding Office action, claims 53-59 and 62-67, 70, and 71 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,437,267 to Weinstein *et al.* (hereinafter "Weinstein") and Published U.S. Patent Application Publication No. US 2001/0004644 A1 to Levin (hereinafter "Levin") in view of Ward-Smith in Nasal Spray Testing, Pharmaceutical Technology Europe (2002) pages 1-9 (hereinafter "Ward-Smith"). In addition, it appears that the Office also relied upon certain product information for Stadol NS®.

Claim 53 is directed to an intranasal unit-dose delivery device comprising one or more sealed vessels containing a sterilized, preservative-free pharmaceutical composition. The composition comprises an effective amount of an opioid and a liquid nasal carrier, wherein upon positioning the device 5 cm away from a laser beam detection pathway, actuating the device to produce a spray plume perpendicular to said pathway, and detecting droplet size distribution of the spray plume with said laser beam detection pathway, the spray plume has a Dv10 of from about 14.3 μm to about 17.1 μm and a Dv50 of from about 31.0 μm to about 35.3 μm.

The Office action states "applicant is completely silent about the *particular* plume geometry that should be produced in order to provide the unexpected results allegedly described in Example 1." Office action page 3. The Office action further states "the references (already of record) of Weinstein, Levin, and Ward-Smith in combination or incorporated together teach the subject matter of the claimed invention." Office action page 2. The Applicant respectfully traverses this rejection.

The particular spray plume geometry from Example 1 is described in detail on pages 10-11 of Preliminary Amendment A, filed October 5, 2005. Applicant indicated previously that the features of the plume geometry are *inherent* in the device tested in Example 1. As illustrated in Figure 1, *this particular spray plume provides* an unexpectedly higher butorphanol concentration in the blood plasma relative to the prior art, multi-dose device.

Applicant also submits that the references applied by the Office action neither teach nor describe how to make the particular intranasal unit-dose delivery device as claimed

herein having the spray characteristics, which as identified by the Applicant, provide unexpectedly better drug delivery. More specifically, Applicant submits that the skilled artisan, based on the teachings of the applied references, would have had no reason whatsoever to believe that using a spray plume with such features could provide unexpectedly higher butorphanol concentrations in the blood plasma relative to the prior art, multi-dose device.

Applicant submits that spray plume geometry is an important feature on how quickly and how much of the therapeutic agent is absorbed through the nasal mucosa following intranasal administration using a unit-dose delivery device. Moreover, spray plumes can have widely different features, e.g., differences in the droplet size at specific distances from the end of the spray nozzle, and differences in the width (i.e., the span) of the spray plume as it advances from the end of the spray nozzle. Each of these features have a profound effect on the pharmacokinetics of drug delivery. Applicant has discovered that the particular plume geometry claimed has an important and beneficial effect on the intranasal administration of an opioid containing composition. The references applied by the Office action do not teach, nor do they describe how to make, the claimed opioid-containing device that produces a spray plume with a droplet size distribution characterized by a "Dv10 of from about 14.3 μm to about 17.1 μm and a Dv50 of from about 31.0 μm to about 35.3 μm" measured as specified by claim 53 and the claims depending therefrom.

The Office action relies upon excerpts from Ward-Smith relating to the *measurement* of spray plume droplet sizes using a "Spraytec with Nasal spray Actuator" which purports to be capable of "allowing measurements in the 1-400[micro]m size range." Office action page 7. However, Ward-Smith does not teach an opioid-containing unit-dose delivery device capable of consistently generating a spray plume with a droplet size distribution characterized by a "Dv10 of from about 14.3 μm to about 17.1 μm and a Dv50 of from about 31.0 μm to about 35.3 μm" when measured as specified in claim 53. Indeed, Ward-Smith is completely silent as to how one could *make* such a unit-dose delivery device. Weinstein and Levin do not cure this deficiency.

The Office action also asserts that "one of ordinary skill in the pertinent art would at once recognize the necessity to properly adjust the ranges." Office action page 8. Assuming for the sake of argument that this is true (which Applicant submits is not the case), the Office action is silent as to how one of skill in the art would know how to modify the spray devices or formulations described in Weinstein, Levin and Ward-Smith in order to make a unit-dose delivery device capable of producing the spray plume required by claim 53, and further specified by the claims depending from claim 53. As described above, Ward-Smith only discusses how to *measure* certain features of a spray plume, but provides no guidance whatsoever on how to design a unit-dose delivery device capable of producing a spray plume as characterized in the instant claims. Applicant, therefore, submits that the skilled artisan would have had no reason to produce a spray plume defined by the claims of the instant invention. Even if so motivated, Applicant believes that the skilled artisan would have no reasonable expectation of being able to successfully make the subject matter encompassed by claim 53, and further specified by claims depending therefrom.

Claims 54-59, 62-67, 70, and 71, depend from 53 and, therefore, incorporate all the limitations of claim 53. In view of the remarks relating to claim 53, Applicant respectfully requests that the rejection of claims 54-59, 62-67, 70, and 71 also be reconsidered and withdrawn.

Rejection of Claims 60, 61 and 72 Under 35 U.S.C. § 103(a)

According to pages 9-10 of the outstanding Office action, claims 60, 61 and 72 stand rejected under 35 U.S.C. § 103(a) as being obvious over Illum *et al.* in J. Pharmacol. Exp. Therapeutics (2001) 301: 391-400 (hereinafter "Illum"), Pezron *et al.* in (Expert Opin. Ther. Patents (2002) 12: 331-340 (hereinafter "Pezron"), Mansjushree *et al.* in Can. J. Anesth. (2002) 49: 190-193 (hereinafter "Mansjushree") in view of U.S. Patent No. 6,127,385 to Midha *et al.* (hereinafter "Midha"). Applicant respectfully traverses the rejection.

Claims 60, 61 and 72 depend from and, therefore, incorporate all the limitations of independent claim 53, such as the limitation of a spray plume characterized by "a Dv10 of from about 14.3 μm to about 17.1 μm and a Dv50 of from about 31.0 μm to about 35.3 μm" measured as specified in claim 53. The arguments relating to claim 53 are reiterated here.

The references applied in the Office action, either alone or in combination, fail to describe all of the features required by claims 60, 61 and 72.

Accordingly, Applicant submits that the applied references fail to teach or suggest the claimed subject matter, taken as a whole. As a result, Applicant respectfully requests that this rejection be reconsidered and withdrawn.

CONCLUSION

Applicant believes that all rejections have been addressed, and early favorable action is respectfully solicited. The Office is invited to contact the undersigned with any questions about this submission.

Respectfully submitted,

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